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Name of Journal: *World Journal of Psychiatry*

Manuscript NO: 74223

Manuscript Type: ORIGINAL ARTICLE

Observational Study

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Treatment outcome, cognitive function and psychopathology in methamphetamine users compared to other substance users

Substance abuse and treatment

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Abstract

BACKGROUND

The rising number of people using methamphetamine leads to an increasing need for treatment options for this patient group. Evidence-based research on the efficacy of treatment programs for methamphetamine users is limited. Due to specific characteristics of methamphetamine users the question arises whether established treatment methods for individuals using other substances can be effective for the treatment of methamphetamine dependence as well. We hypothesize that there are significant differences between the two groups that may affect the effectiveness of treatment and worsen the prognosis of treatment outcomes for methamphetamine users compared to consumers of other substances.

AIM

To investigate potential differences in cognitive functioning and psychopathology between methamphetamine users and other substance users and possible correlations with treatment outcomes.

METHODS

A total of 110 subjects were recruited for an observational longitudinal study from a German inpatient addiction treatment center: 55 patients with methamphetamine dependence and 55 patients with dependence of other substances ("OS group"). Both groups were examined at beginning (baseline) and end of treatment (after six months) with regard to treatment retention, craving, cognitive functioning, psychosocial resources, personality traits, depression and other psychiatric symptoms. Instruments used were Raven's IQ test, Mannheimer craving scale, cognitive test battery, NEO personality factors inventory, Hamilton depression scale, Becks depression inventory and symptom checklist. The statistical methods used were chi²-test, t-test and multiple mixed ANOVAS.

RESULTS

A total drop-out rate of 40% (Methamphetamine-group: 36.4%; OS-group: 43.6%) was observed without significant differences between groups. At baseline, Methamphetamine-group subjects significantly differed from OS-group individuals in terms of a lower intelligence quotient, less years of education, poorer working speed and lower working accuracy as well as less cannabinoid and cocaine use. Methamphetamine-group subjects further showed a significantly lower score of conscientiousness, depressive and psychiatric symptoms than subjects from the OS-group. In both groups a reduction of craving and depressive symptoms and an improvement of working speed and working accuracy was noted after treatment.

CONCLUSION

There are differences between methamphetamine users and users of other drugs, but not with regard to the effectiveness of treatment in this inpatient setting. There are differences in cognitive function and psychopathology between methamphetamine and other drugs users. The existing treatment options seem to be an effective approach in treating methamphetamine dependence.

Key Words: Treatment outcome; cognitive function; psychopathology; methamphetamine; substance use; comparison

Kamp F, Behle N, Proebstl L, Hager L, Riebschläger M, Schacht-Jablonowsky M, Hamdorf W, Neumann SN, Krause D, Manz K, Franke AG, Koller G, Soyka M. Treatment outcome, cognitive function and psychopathology in methamphetamine users compared to other substance users. *World J Psychiatry* 2022; In press

Core Tip: There are differences between methamphetamine users and users of other drugs, but not with regard to the effectiveness of treatment in this inpatient setting. The

existing treatment options seem to be an effective approach in treating methamphetamine dependence.

INTRODUCTION

The United Nations estimate that about 27 million people worldwide regularly abuse amphetamine-type stimulants (ATS) in 2018³⁸ (World Drug Report, 2021). Especially the rising number of people using methamphetamine as the “next addiction crisis”²⁶ (Paulus and Stewart 2020) causes growing concern³⁸ (World Drug Report, 2021). Accordingly, there is a growing need for evidence-based treatment options for methamphetamine users^{14,26} (Hamdorf *et al*, 2015; Paulus and Stewart 2020). ¹ Evidence-based research on the efficacy of treatment programs for methamphetamine users is still limited⁸ (Drogenbeauftragte der Bundesregierung *et al*, 2016) with no established pharmacotherapy available^{6,26} (Chan *et al* 2019, Paulus and Stewart 2020). The question arises whether established treatment methods for individuals using other substances can be effective for the treatment of methamphetamine dependence as well. This question is important, since – until a few years ago – methamphetamine use played a minor role in German substance treatment services and therefore most methamphetamine users are treated in institutions having a focus on other drugs of abuse such as alcohol, opioids, amphetamine, or cocaine. However, representative studies comparing the characteristics of methamphetamine users to users of other substances are limited. A study based on expert interviews and focus groups on characteristics of methamphetamine consumers showed that they differ from users of other stimulants with respect to higher levels of dissocial behavioral (e.g. aggressiveness, impulsiveness, egoism or irritability) as well as emotional instability, unreliability and other comorbidities¹⁷ (Hoffmann, Buchenauer, Schumann, Schröder & Martin, 2019). The authors also reported that the therapy of methamphetamine users is substantially affected by their comorbidities and stated, that the provided rehabilitation for methamphetamine users in Germany is inadequate, resulting in a need to adapt the treatment concepts for this group¹⁷ (Hoffmann *et al*, 2019). Meanwhile a smaller study²⁷

($n = 31$) was published by Petzold *et al* (2021). Another study also showed that methamphetamine use seems to be associated with co-occurring substance use and mental illness¹⁹ (Jones, Compton & Mustaquim, 2020). This may be of relevance as reviewed comorbidities were frequently associated with worse treatment outcomes³³ (Kuitunen- Paul, Roessner, Basedow & Golub, 2021). The available data demonstrate that the rise in methamphetamine use and harms is intimately linked to the ongoing opioid crisis. The concurrent use of opioids and methamphetamines may decrease adherence to short-term residential treatment. Accordingly, effective strategies should be identified to retain individuals who use opioids and methamphetamines concurrently in treatment^{20,39} (Jones, Houry, Baldwin, Vivolo-Kantor & Campton, 2021; Ware, Manuel & Huhn, 2021). In addition, there are also data suggesting methamphetamine to cause neural damage and persistent forms of cognitive impairment, including deficits in attention, memory and executive function¹ (Barr, Panenka, MacEwan *et al*, 2006). These results are in line with other studies also indicating that methamphetamine users may differ from other substance users with respect to cognitive function^{29,30} (Potvin *et al*, 2018; Proebstl *et al*, 2018). This may be important in terms of treatment outcome, since for example Bernhardt *et al* (2020) reported correlations between methamphetamine treatment outcome and the recovery of cognitive impairment² (Bernhardt, Petzold, Groß *et al*, 2020).

Another study found an association between a low level of perceived social support and methamphetamine dependence¹⁸ (Jalali, Shabrandi, Jalali & Salari, 2019). However, the authors also found an association between moderately (and not distinct) pronounced personality factors (agreeableness, neuroticism, extraversion, conscientiousness and openness) and methamphetamine use¹⁸ (Jalali *et al*, 2019). A systematic review of psychological treatments for methamphetamine use disorders states that focusing more on the helping-relationship categories is a key approach for increasing the efficacy of treatments for methamphetamine use²⁸ (Phukao, 2021).

These studies have been mostly of exploratory nature and were investigating exclusively methamphetamine users, but without direct comparison to other drug

users. In this study, we focus on factors such as cognition, personality traits, comorbidities, psychiatric symptoms and psychosocial resources and their implication on treatment outcome. Based on limited previous research, one may assume that methamphetamine users have more neuropsychiatric symptoms compared to users of other substances. Specifically, a higher rate of comorbid psychiatric symptoms and disorders, a lower level of cognitive functioning and limited psychosocial resources and finally lower retention rate in treatment in methamphetamine users can be postulated. This exploratory study focuses on these possible differences in primary methamphetamine users compared to users of other substances. We hypothesize that there are significant differences between the two groups that may affect the effectiveness of treatment and worsen the prognosis of treatment outcomes for methamphetamine users compared to consumers of other substances.

MATERIALS AND METHODS

MATERIALS AND METHODS

Participants and treatment program

All participants were inpatients at a hospital specialized for treatment of substance use disorders (MEDIAN Klinik Mecklenburg) and were recruited by psychologists and physicians ¹ during the first two to four weeks after admission. Participation was voluntary. The treatment was set up for six months and the interventions were applied as individual and group therapy, with the main focus on group sessions (five times per week). Table 1 shows details about the treatment concept. Main treatment goals were the analysis of triggers for craving and the development of new behavioral strategies for coping with craving and other substance related problems. The two-week initial phase aimed at completion of diagnostics, establishment of self-reflection and motivational support and finally defining therapy goals. During the twenty-two-week core treatment phase, interventions as for example psychoeducation, situation and trigger analyses, mindfulness strategies and assertiveness training were applied. The last two weeks

focused on relapse prevention and aftercare. For further details see also³⁴ Soyka, Koller, Proebstl *et al*, (2017).

Inclusion criteria were a history of methamphetamine abuse or addiction (meeting the respective ICD-10 criteria) for the primary methamphetamine user group and a history of abuse or dependence of other substances for the other substances group ("OS group"). Because polydrug use is very common⁷ (Crummy *et al*, 2020) Methamphetamine-group participants were included when having a history of previous use of other substances, but methamphetamine had to be the primary drug of abuse and main reason for admission to treatment. See table 2 for information about the history of substance use in both groups.

Minimum age was 18 years. Exclusion criteria were acute psychotic symptoms, intoxication on test days and insufficient comprehension of study materials or procedure. Informed written consent was obtained from all participants after a complete and extensive description of the study protocol. The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich. All participants were financially reimbursed with 15 Euro after completion of assessments. Routine urine samples and breath alcohol tests were collected to verify substance use. These tests were part of the usual hospital practice and were conducted by the clinic staff on a sample basis and in case of suspected substance use.

Study Design

The observational longitudinal study was designed to capture within and between group differences at two time points: "T0" Baseline at the beginning of treatment and "T1" at the end of treatment, after approximately 24 wk. The T1 assessment took place during the last 3 wk before discharge and the exact time point varied individually. Both surveys were conducted by trained staff. Data were collected between November 2016 and June 2018 for the Methamphetamine-group and between June 2018 and February 2019 for the OS-group. See figure 1 for details.

Outcome Measures and Instruments

The main outcome of interest was the completion of treatment as scheduled (regular discharge). Individuals stopping treatment prematurely (at own request or as a disciplinary decision) were defined as dropouts. A positive urine test result was classified as a non-reported relapse, which led to a disciplinary dismissal.

Further outcomes of interest were differences between Methamphetamine- and OS-group and between time points T0 and T1. These differences include craving, cognitive functioning, psychosocial resources, depression and other psychiatric symptoms, as well as personality traits (only measured at baseline). Table 3 displays the used instruments at the respective assessment.

Statistical Analyses

Continuous variables were summarized by their mean (m) and standard deviation (SD), categorical variables by absolute (n) and relative frequencies (%). Group comparisons were performed using chi²-test (for categorical variables, or in case of small cell numbers, Fisher's exact test) and t-test (continuous variables). Multiple mixed ANOVAs were calculated to compare mean differences between substance groups taking into account both time points (T0 and T1). Since t-tests and ANOVAs are regarded as robust statistical procedures, both methods were also used for variables potentially deviating from the normality assumption. Univariable logistic regression models were applied to investigate the effect of independent factors on treatment drop-out. Odds ratios (OR) are reported together with their 95% confidence intervals (CI). The significance level was set at $p = .05$ and no p value adjustment for multiple testing was applied in this explorative study. All statistical analyses were conducted in SPSS Version 24.

RESULTS

RESULTS

Participants' flow and treatment completion

A total of 110 participants (55 in each group, 89 men and 21 women) with a mean age of 30.95 years (SD= 6.65) were included in the first assessment at T0. There were no statistically significant differences in age (30.0 vs. 32.0 years, $p = .12$) or gender

distribution (76.4% vs. 85.5% males, $p = .23$) between Methamphetamine- and OS-groups. Out of this original sample, 18 subjects refused to take part in further assessments after T0 and 55 subjects (27 from Methamphetamine, 28 from OS-group) participated again in the second measurement T1 with a mean age of 30.0 years ($SD = 6.43$). Again, the majority of T1 subjects was male (45 men, 10 women) and there was no significant difference in gender distribution ($p = .50$).

From the baseline sample, 66 subjects (60%) completed the treatment while 44 individuals (40%) dropped-out of treatment. Comparison of the Methamphetamine-group and the OS-group revealed no significant difference in drop-out rates (36.4% vs. 43.6%, $P = 0.44$). In addition, there was neither a significant difference in age ($p = .19$) nor in gender distribution ($P = 0.84$) between drop-outs and completers.

The most common reason for treatment drop-out was at own request (42.2%), followed by violation of institution rules (26.7%), unreported relapse during treatment (24.4%) and transfer to another treatment center (6.7%). There was no significant association in the reasons for drop-out between Methamphetamine and OS-group ($p = .21$).

Participants remained in treatment for a mean time of 147 days ($SD = 68$). There was a trend towards a longer treatment retention in the Methamphetamine-group compared to OS-group, but this difference failed to reach statistical significance (159 ($SD = 60$) vs. 135 days ($SD = 73$), $p = .07$). The OS group attended a slightly higher mean number of group sessions (OS: 103 ($SD = 57$); Methamphetamine: 87 ($SD = 35$), $p = .07$), while the Methamphetamine-group had a slightly higher mean number of individual therapy sessions (Methamphetamine: 27 ($SD = 18$); OS 22 ($SD = 13$), $p = .08$). However, both differences were not statistically significant. A mean treatment duration of 93 days ($SD = 57$) was found among the patients dropping out of treatment.

Baseline comparisons of Methamphetamine and OS-group characteristics

Methamphetamine-group subjects had less years of education than OS-group subjects ($p = .048$) and showed a significantly lower mean intelligent quotient (Raven's IQ=93.7) at baseline than the OS- individuals (IQ= 100.1, $p = .02$, see also table 4).

Methamphetamine-group participants also performed poorer on both measures of the cognitive test battery Cognitrone, resulting in a significantly lower working speed ($p = .002$) and working accuracy ($p = .03$) compared to OS-subjects. Methamphetamine- and OS- subjects showed no significant differences with respect to employment ($p = .19$) or partnership during the last six months prior to admission ($p = .46$).

Participants from the Methamphetamine-group showed a significantly lower score of the personality trait conscientiousness (measured by the NEO-Five-Factor-Inventory) compared with subjects from the OS-group ($p = .04$). No other personality traits differed significantly between both groups. The OS group showed significantly higher Hamilton Depressive Rating Scale (HAMD) ($p = .04$) and Symptom Checklist (SCL) depression ($p = .03$) – but not Beck Depression Inventory-II (BDI- II) ($p = .17$) – mean scores at treatment begin than the Methamphetamine-group. The OS-group also had a higher mean score of the SCL “Positive Symptom Distress Index” (PSDI), a measure of intensity of present symptoms, compared to the Methamphetamine-group ($p = .02$). There were no statistically significant differences in Attention Deficit Hyperactivity Disorder (ADHD) scores ($p = .56$), craving ($p = .87$) or psychosocial resources ($p = .69$) at baseline.

As explained, methamphetamine-group subjects may have had a history of other drug use, but methamphetamine had to be the prior substance. The majority of all subjects also used cannabinoids, but the number of cannabinoid users was significantly higher in the OS-group than in the Methamphetamine-group ($p = .04$, see table 2). The OS-group also included a significantly higher number of individuals that used cocaine ($p = .001$), while there were no differences in the use of other substances. There was no significant difference between groups concerning the number of previous substance use treatments ($p = .98$).

Regarding the number of comorbid psychiatric diagnoses (measured by ICD-10), a significantly higher rate in anxiety disorders ($p = .03$) and somatoform disorders ($p < .0001$) was found in Methamphetamine-group patients, while there was a higher rate of other psychotic disorders in OS-group participants ($p = .04$, see table 5).

Comparisons of groups over time

Mixed ANOVAs were used to compare the cognitive functioning over time and between groups. The working speed significantly improved from T0 to T1 in both groups ($p < .001$, see also table 6) and there was a significant group effect for both measurements, showing a better performance in the OS- than in the Methamphetamine group in working speed ($p < .001$, see figure 2). There was no interaction effect ($p = .94$). Regarding working accuracy, there also was a significant improvement of performance over time in both groups ($p < .001$). The OS-group showed a higher working accuracy at both times, but this effect was not statistically significant ($p = .43$). Again, there was no interaction effect ($p = .79$, see figure 2). Both groups showed a significant reduction of the intensity of psychiatric burden, as measured by the SCL-90-R PSDI score, over time ($p < .001$). The OS-group showed a greater decrease than the Methamphetamine-group (see figure 3), but the interaction effect failed to reach statistical significance ($p = .07$). The groups did no longer differ significantly over time ($p = .29$). SCL-90-R depression scores ($p < .001$) and HAMD depression scores ($p = .001$) were significantly decreased over time in both groups. However, taking baseline and T1 assessment together, the difference between OS- and Methamphetamine-group was no longer significant (SCL depression score: $p = .09$; HAMD: $p = .09$). Again, no interaction effects were found (SCL depression score: $p = .97$; HAMD: $p = .66$, see figure 4). Analyzing the BDI-II depression scores also revealed a significant reduction of depression scores over time ($p < .001$), but without interaction ($p = .81$) or group effect ($p = .56$). Similar results were seen regarding craving scores with a significant reduction over time ($p < .001$), without interaction ($p = .94$), and without group effect ($p = .86$). We found a significant increase of psychosocial resources over time ($p = .048$), but again, no significant differences between both groups ($p = .99$) and no interaction effect ($p = .71$).

Predictors of treatment drop-out

Neuroticism measured at baseline was a significant predictor for treatment drop-out in the whole sample, showing decreasing odds for drop-out with increasing neuroticism scores (OR = .93, 95%CI: [.87, .99], $p = .03$). No other baseline personality variables

predicted treatment drop-out. Higher scores in Cognitrone working accuracy, measured at baseline, also significantly predicted a treatment drop-out (OR= 1.05, 95%CI: [1.0, 1.09], $p = .04$), while working speed was no significant predictor ($p = .20$). Raven's IQ ($p = .90$), Craving at baseline ($p = .99$), as well as SCL depressive scores ($p = .10$) were no significant predictors of drop-out.

DISCUSSION

DISCUSSION

The present study found differences between methamphetamine and other drug users in terms of cognitive function, psychiatric comorbidities, and personality traits, but not regarding treatment outcome and retention. The latter finding suggests that despite the encountered differences between methamphetamine users and other drug users, methamphetamine users do not perform worse than other drug users in currently provided treatments. This result raises the question if there is need for new and specialized treatment options for methamphetamine users. For example, patients may have reported especially methamphetamine related situations or consequences when reflecting their use patterns and for example possible relapse situations. Previously, in another longitudinal study, we compared the methamphetamine group from this study with another methamphetamine user group, that received a more stimulant specific treatment²¹ (Kamp *et al*, 2019). We found no differences in treatment retention or long-term relapse rates between both groups, which supports the hypothesis that methamphetamine users may not benefit automatically from a more stimulant specific treatment. Study results reveal that a high number of methamphetamine users use other substances, too. These patients may benefit from existing treatments.

Interestingly, the present study revealed a trend (although not statistically significant) towards longer treatment duration of approximately 20 days in the methamphetamine group, which may indicate that methamphetamine users may have a greater benefit from the investigated treatment. However, with regards to all other treatment outcome measures, we did not find any relevant interaction, which suggests that both groups

overall benefited from treatment. For example, both groups showed a reduction of craving, depression scores and overall psychiatric burden (measured by SCL-90R) and an improvement in working speed and working accuracy as well as an increase of psychosocial resources at the end of the treatment compared to its initiation. Therefore, it can be concluded that a current “treatment as usual” inpatient addiction program is helpful for methamphetamine users *and* users of other substances and that both user groups do not differ from each other in their response to the treatment.

Nevertheless, this study did reveal differences between methamphetamine users and other substance users, for example with respect to cognitive function. Neurotoxic effects of metamphetamine use are well established²⁶ (Paulus and Stewart 2020). As we hypothesized, methamphetamine users had significantly lower baseline intelligence quotient, poorer working speed and lower working accuracy compared to users of other drugs. This finding confirms results from other studies indicating that methamphetamine use can impair cognitive functions²⁹ (Potvin *et al*, 2018; Proebstl *et al*, 2018). However, school education was lower in the Methamphetamine-group, raising the question of whether impaired cognitive function in the Methamphetamine-group is a reason for or rather a consequence of methamphetamine use. Unfortunately, there are no longitudinal data to further explore this point. A previous study failed to show improvement of cognitive impulsivity deficits in metamphetamine users after short term abstinence of six weeks¹⁰ (Fitzpatrick *et al* 2021). Furthermore, the performance of the Methamphetamine user group was still in the average range, when applying the test norms (t-values) and we had no matched control group without drug users to clarify the differences between both groups. Interestingly – and contrary to our hypothesis – higher scores in working accuracy at baseline were associated with a higher likelihood for treatment drop-out. Other studies that have examined ADHD patients have found lower accuracy scores as significant predictors of drop out and mild cognitive deficits which is in contrast to the results of this study³⁵ (van Emmerik-van Oortmerssen *et al*, 2020). Furthermore, we did not find an effect of working speed and IQ on treatment

retention, which makes it difficult to generalize the impact of cognitive performance on drop-out rates.

Again, as assumed, Methamphetamine-patients had a higher rate of comorbid anxiety and somatoform disorders. But contrary to this result, OS- group participants showed a higher rate of psychotic disorders and there were no differences between both groups in terms of other comorbidities. Therefore, different substance use patterns may be associated with different comorbidities, but not in this study.

Another unexpected result was the negative association between neuroticism and treatment drop-out. The higher the score for neuroticism, the lower the odds of treatment drop-out. Other studies conclude, contrary to our results, that emotional instability and high neuroticism scores are risk factors for relapse at least in alcohol users⁴ (Bottlender & Soyka, 2005). Treatment dropouts in a program for cocaine addiction showed a higher score on histrionic and antisocial scales compared to completers⁹ (Fernandez-Montalvo & López-Goñi, 2010). Since it can be assumed that histrionic as well as antisocial personality traits tend to be associated with higher neuroticism, this result is also not consistent with our finding. We are not aware of any studies that specifically examined neuroticism as a predictor of addiction treatment dropout.

Our study has several limitations. For example, we did not correct the analyses for multiple testing, as this study was designed to generate hypotheses for future research on possible differences between Methamphetamine- and OS patients.

Furthermore, in the group that used other substances, amphetamine use was not an exclusion criterion. Even though the two substances are very similar, it has been suggested that methamphetamine has a stronger effect on the dopamine transporter mediated cell physiology than methamphetamine; therefore, the latter has a higher addictive potential¹³ (Goodwin *et al*, 2009).

Beyond that, the reported treatment effects are limited to the sample of treatment completers. Regarding the therapeutic outcome of the drop-out patients, there were no available data for T1, and therefore the treatment effects for the drop-out sample remain

unclear. Especially, there are not enough information on patients who stopped treatment at their own request. The present study showed that the average time patients spend in treatment before they dropped out is still quite high (around three months). It remains unclear why they did not continue the treatment. Future investigations covering the whole treatment process may help gaining further informations on characteristics of later drop-outs with focus on craving, treatment satisfaction and value of therapeutic relationship^{5,22,24} (Meier *et al*, 2006; Kelly *et al*, 2010; Brorson *et al*, 2013).

CONCLUSION

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There are differences between methamphetamine users and users of other drugs, but not with regard to the overall effectiveness of a six-month inpatient addiction treatment. Both groups showed a reduction in psychiatric symptoms over time and improved cognitive function after treatment compared to treatment begin. Methamphetamine users therefore seem to benefit from existing, stimulant nonspecific treatment options in a similar way than other drug users do.

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SIMILARITY INDEX

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